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Pharmacogenetic testing prior to carbamazepine treatment of epilepsy: 1 patients' and physicians' preferences for testing and service delivery

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British Journal of Clinical Pharmacology

DOI:
10.1111/bcp.12715

Published: 03/07/2015

Peer reviewed version

Cyswllt i'r cyhoeddiad / Link to publication

Dyfyniad o'r fersiwn a gyhoeddwyd / Citation for published version (APA):
Powell, G., Holmes, E. A., Plumpton, C. O., Ring, A., Baker, G. A., Jacoby, A., Pirmohamed, M., Marson, A. G., & Hughes, D. A. (2015). Pharmacogenetic testing prior to carbamazepine treatment of epilepsy: 1 patients' and physicians' preferences for testing and service delivery. *British Journal of Clinical Pharmacology*, *80*(5), 1149-1159. https://doi.org/10.1111/bcp.12715

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04. May. 2023

Title: Pharmacogenetic testing prior to carbamazepine treatment of epilepsy: patients' and physicians' preferences for testing and service delivery

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Running title: Genetic testing preferences in epilepsy

Keywords: Carbamazepine, pharmacogenetics, cutaneous adverse drug reaction, discrete choice experiment, HLA-A*31:01

Word count (text): 3576

Number of figures: 1

Number of tables: 5

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Summary

Aim: Pharmacogenetic studies have identified the presence of the *HLA-A*31:01* allele as a predictor of cutaneous adverse drugs reactions (ADRs) to carbamazepine. This study aimed to ascertain the preferences of patients and clinicians to inform carbamazepine pharmacogenetic testing services.

Methods: Attributes of importance to people with epilepsy and neurologists were identified through interviews and from published sources. Discrete choice experiments (DCEs) were conducted in 82 people with epilepsy and 83 neurologists. Random-effects logit regression models were used to determine the importance of the attributes and direction of effect.

Results: In the patient DCE, all attributes (seizure remission, reduction in seizure frequency, memory problems, skin rash and rare, severe ADRs) were significant. The estimated utility of testing was greater, at 0.52 (95% CI, 0.19 to 1.00) than not testing at 0.33 (95% CI, -0.07 to 0.81). In the physician DCE, cost, inclusion in the British National Formulary, coverage, negative predictive value (NPV), and positive predictive value (PPV) were significant. Marginal rates of substitution indicated that neurologists were willing to pay £5.87 for a 1 percentage point increase in NPV and £3.99 for a 1 percentage point increase in PPV.

Conclusion: The inclusion of both patients' and clinicians' perspectives represents an important contribution to the understanding of preferences towards pharmacogenetic testing prior to initiating carbamazepine. Both groups identified different attributes but had generally consistent preferences. Patients' acceptance of a decrease in treatment benefit for a reduced chance of severe ADRs adds support for the implementation of *HLA-A*31:01* testing in routine practice.

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What is known about this subject:

- Carbamazepine is associated with severe, immune-mediated adverse drug reactions that may be predicted, and potentially avoided, by testing for human leukocyte antigen alleles
- There is presently no evidence on the preferences of patients with epilepsy or neurologists towards pharmacogenetic testing prior to carbamazepine treatment

What this study adds:

- Based on discrete choice experiments, patients were willing to accept a reduced chance of 1-year remission from seizures for a reduction in adverse drug reactions
- Neurologists' preference for testing was sensitive to the cost of the test, but they were willing to pay for a modest increase in negative predictive value

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Introduction

Carbamazepine is used widely as a first-line treatment for focal onset seizures, and has proven benefits in terms of time to achieving 12-month remission [1,2]. However, it is associated with common adverse drug reactions (ADRs) [3] and more serious, immune-mediated ADRs, including cutaneous hypersensitivity reactions such as Drug Induced Hypersensitivity Syndrome (DIHS), Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). The estimated incidence of SJS-TEN is 1 to 6 per 10,000 persons exposed to carbamazepine with TEN being associated with mortality of up to 30% [4].

Pharmacogenetic association studies have identified significant genetic predictors of cutaneous ADRs associated with carbamazepine. While rare in European populations, the *HLA-B*15:02* allele is a significant predictor of SJS-TEN in people of Han-Chinese descent [5], and testing significantly reduces the rate of SJS-TEN [6]. Recommendations from regulators have consequently led to increased use of *HLA-B*15:02* testing of people of Han-Chinese, Thai and other Asian origin in East Asia.

In European populations, the *HLA-A*31:01* allele is a significant predictor of the full spectrum of carbamazepine-induced hypersensitivity ADRs [7], the risk being 26% in carriers of the allele and 3.8% in non-carriers. Based on the 10% prevalence of mild carbamazepine-induced cutaneous ADRs (maculopapular exanthema) in people of European descent [1], 39 people would need to be screened to prevent one carbamazepine-induced ADR [7]. However testing for *HLA-A*31:01*, which has a prevalence of 2 to 5% in European populations, has yet to gain mainstream acceptance in Western countries. As for any new innovation, uptake will be dependent on many factors, not least patients' acceptance, and preferences for harm reduction versus benefit maximisation; and prescribers' considerations of diagnostic value, clinical utility and cost, among other factors [8].

Discrete choice experiments (DCEs) are a method for measuring respondents' stated preference for healthcare interventions or services [9]. In DCEs, respondents are asked to choose their preferred

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alternative from a set of hypothetical (but realistic) alternatives. The method allows for the estimation of the relative importance of different aspects of care, assessment of any trade-offs between these aspects, and of respondents' total satisfaction (utility) associated with the intervention or service under consideration [9,10]. DCEs have been used previously to elicit preferences for antiepileptic drugs (AEDs) [11,12] and for the delivery of pharmacogenetic testing services [13]. The latter revealed differences in patient and prescriber preferences, with patients demanding accurate and timely information regarding why testing was necessary and what the test results meant, while health-care professionals focussed more on the predictive accuracy and waiting time for a test result [13].

In the present study, we aimed to ascertain the preferences of patients with epilepsy and neurologists when considering testing for *HLA-A*31:01* prior to prescribing carbamazepine. Specifically, we estimated patients' threshold at which the incidence of serious ADR would make testing worthwhile and neurologists' willingness to pay for testing. The results of this study may inform the delivery of pharmacogenetic testing services.

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Methods

Overview

We identified attributes that patients with epilepsy and neurologists considered important in their respective consideration of pharmacogenetic testing prior to starting treatment with carbamazepine. Levels for each attribute were derived from appropriate sources of clinical evidence. Separate DCEs were designed and administered to samples of patients with epilepsy and neurologists from across the UK.

Participants and administration

Adults aged 18 or over and who self-reported as being diagnosed with epilepsy by a doctor were eligible. Participants were not rewarded for their time but were informed of the potential benefits and risks to them, and had to consent before taking part. Recruitment was facilitated by the UK charity Epilepsy Action and included advertisements, articles and links using social media, members' magazine, e-forums and newsletters, and website home page. An advertisement was placed in the local press and posters displayed in hospital clinics. The questionnaire was made available via a link to an anonymous online service (Snap Surveys, London, UK) between June and October 2013. Target sample size was 63 completed DCE responses, based on each main effect level of interest being represented across the design at least 500 times [14]. Ethical approval was gained from the NHS National Research Ethics Service (reference 11/NW/0191).

Adult and paediatric neurologists registered in the UK were recruited via the International League Against Epilepsy and the Association of British Neurologists. The questionnaire was made available nationally via an anonymous online service (SurveyMonkey, Palo Alto, CA) between July and October 2012. The target sample size for the main effects analysis was 47 completed DCE responses [14].

Attribute and level selection

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Attributes for the patient DCE were identified using semi-structured interviews with patients, focus group with prescribers, and from published data. Patients (n=56) were recruited from three clinical sites, and included 33 with established epilepsy (17 females, mean age 38 years) and 23 with a recent (≤1 year) diagnosis of epilepsy (10 females, mean age 43 years). Forty-one patients were first asked to list and rank attributes relating to the benefits, side-effects and life-impacts of treatment for epilepsy. The second stage of the interviews was designed to explore the framing of risk and the validity of risk communication. Fifteen patients participated in cognitive interviews to assess the face validity of the DCE (presentation of attributes and levels) and were provided with show-cards depicting risk in pictograms alongside a written explanation of the risk being illustrated. Interviewers were given notes on how to explain risk. This exercise was repeated in the focus group with prescribers (n=8), who were also asked to discuss the frequency and severity at which side-effect became a 'clinically important adverse event' that would require a change in treatment. Prescribers were also asked for feedback on the format of the patient DCE and the presentation of attributes and levels. The final DCE of patients contained 5 attributes to represent remission of seizures (the highest ranked benefit in the qualitative study), reduction in seizure frequency, memory problems (the highest ranked side-effect in the qualitative study), skin rash, and rare or uncommon severe ADRs (associated with carbamazepine) (Table 1). Appropriate levels for each category were identified from published clinical data [1,7,15].

Insert Table 1 here

Attributes for the physician DCE were taken from Payne et al. [13], who identified cost, predictive accuracy and result turnaround time as being important when considering pharmacogenetic tests; and from structured individual interviews with neurologists (n=12) recruited from the North West of England. Initial interviews involved a discussion of attributes that would be of potential importance to neurologist when considering a pharmacogenetic test and included: cost, predictive accuracy, turnaround time to result, coverage of test (severe ADRs only or severe and mild ADRs), inclusion in

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British National Formulary (BNF) [16], method of testing (blood, salivary swab), method of follow-up and subsequent prescribing, location of testing and method of presentation of results ('raw data', summarised interpretation).

A rating exercise was performed to identify the attributes of greatest importance. Subsequent interviews with neurologists discussed the presentation of the attributes and identified relevant levels. As this study targeted UK neurologists, cost was understood to be total cost to the National Health Service (NHS), rather than cost to the patient or cost for a privately requested test. Although there is no direct cost to the neurologist or patient, neurologists and physicians in general in the UK are cognisant of the costs of medical interventions and this characteristic was confirmed by the identification of the attribute as important in the interviews. Framing of the predictive attributes of the pharmacogenetic test was discussed. The negative predictive value (NPV) and positive predictive value (PPV) were understood and favoured by the neurologists compared to alternative methods of presentation including sensitivity, specificity or 'risk of ADR following test'. The final attributes presented in the DCE were: cost, time to result, inclusion in the BNF, coverage, NPV, and PPV (Table 1). Data from published sources [5,7], together with discussion in individual interviews with neurologists and expert opinion led to identification of a range of plausible attribute levels.

Experimental design

Our qualitative findings did not reveal a common list of attributes that could be used to value both physician and patient preferences for pharmacogenetic testing services. We therefore conducted two separate DCEs that contained the most relevant and plausible attributes from both perspectives.

In clinical practice, patients who test positive for the *HLA-A*31:01* allele would be prescribed an alternative AED, which is likely to have a different benefit and harm profile. To reflect this, the DCE asked patients to choose between two hypothetical medicines, from which we inferred their

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preference for pharmacogenetic testing. The DCE used a fractional factorial design [18] and folded into eight binary choices, one of which is presented as an example in Figure 1. The DCE was administered as part of a larger survey containing 126 items in total and requiring an estimated 30 minutes for completion

A binary design was selected for the DCE of neurologists in order to include a choice of no testing, which is aligned with current clinical practice. A fractional factorial design was selected from a design catalogue to ensure orthogonality [18]. Sixteen choice scenarios were presented to respondents, following the example shown in Figure 1.

Insert Figure 1 here

Analysis

Random effects logit regression models were used to determine the importance of the attributes and direction of effect. Marginal rates of substitution (MRS, the rate at which respondents were willing to give up a unit change in one attribute in exchange for a unit change in another while maintaining the same level of utility) were calculated using each attribute as the value attribute with Bootstrapped confidence intervals calculated using 1,000 replications. All analyses were conducted in STATA version 10 (StataCorp, College Station, TX). To test the validity of the patient DCE we identified a potentially dominant choice in which medicine A was superior in all but one attribute (higher chance of remission, lower risk of memory problems, mild rash and life-threatening ADR; but a higher frequency of seizures). We assumed that people who selected the alternative (medicine B) for this choice did not understand the task, and analysed the DCE with and without these respondents by comparing the confidence intervals of all the coefficients in the regression to ascertain if there were statistically significant differences.

Patients' utility was calculated by weighting the results of the regression against potential outcomes of treatment with carbamazepine with or without pharmacogenetic testing. Clinical data [1,7,15]

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were used to model the scenarios of testing (in which carriers of the *HLA-A*31:01* allele are prescribed lamotrigine) and standard care (Table 2). The probability of test uptake was calculated as the exponential of the utility for testing divided by the sum of the exponential of the utilities for testing and not testing. We further calculated the threshold at which patients would prefer to be tested, defined when the utility of testing is at least as much as the utility of standard treatment:

$$-\sum_{1}^{N} MRS_{attribute(N)} * \Delta_{attribute(N)} \leq \Delta_{sADR}$$

where, *MRS* is the ratio of beta coefficient for a given attribute divided by the beta coefficient for severe ADRs (*sADR*), and $\Delta_{attribute}$ represents the actual difference in probabilities of occurrence of attribute-defined events between a testing strategy and standard treatment. The trade-off between the benefits and harms of interest provides the point of indifference from the patient's perspective and therefore represents the threshold at which patients would choose to be tested.

Insert Table 2 here

Scenario analyses

While the base case focused on *HLA-A*31:01*, a scenario analysis was performed using the characteristics of testing for *HLA-B*15:02*. This was based on a meta-analysis of the association with SJS/TEN [19] and assumed a 10% allele prevalence, consistent with Asian populations [20].

A further exploratory analysis was conducted by identifying statistically significant subgroups based on log likelihood ratio tests of base case 'restricted model' (all cases) and unrestricted models for groups of n≥30 and assuming p<0.05 with Bonferroni correction.

For the DCE of neurologists, welfare estimates including total utility and probability of uptake were calculated for various testing scenarios which represented: a less expensive test, higher PPV and NPV, and a reduced time to test result. A test which costs £100, takes 4 days for the result, with PPV 26%, NPV 96%, predictive of both severe and mild ADRs but not included in the BNF was selected as

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being representative of current clinical practice associated with *HLA-A*31:01* testing. An assessment of validity using a dominant choice set was not possible in the DCE of neurologists. Pharmacogenetic testing for *HLA-A*31:01* is not currently mandatory and therefore selecting a single scenario where a test should always or never be selected would not be appropriate in the context of a labelled DCE. We defined non-traders as respondents always selecting one response (test or no test) and examined the results of the regression with and without the inclusion of non-traders.

Results

Patients' DCE

Ninety-two people with epilepsy started the DCE, of which 82 (89%) completed the survey. Respondents had a median age of 38 years and 61 (66%) were female (Table 3). Almost all patients were taking AEDs (n=85, 99%) and 31 (36%) had experienced changes to their AED treatment in the previous three months. Over a third of respondents (n=31, 36%) had previously taken carbamazepine to treat epilepsy, of which one respondent reported a severe skin reaction requiring hospitalisation and 10 (19%) had experienced rash of the upper body.

Insert Table 3 here

All 5 attributes were significant and in the expected direction and the overall goodness of fit of the model was good (Table 4). Five patients failed to select the dominant choice, however as there were no statistically significant differences between models by their inclusion or exclusion they were retained in the base case analysis. Patients were willing to accept a reduction in the chance of 12-month remission from seizures in exchange for a reduction in adverse events. Patients were willing to reduce the chance of remission by: 0.58 percentage points (95% CI, 0.39 to 0.82) for a 1 percentage point reduction in skin rash; 3.2 percentage points (95% CI, 2.32 to 4.44) for a 1

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percentage point reduction in memory problems; and, 1.76 percentage points (95% CI, 1.21 to 2.54) for a 0.001 percentage point reduction in the risk of a severe ADR.

Insert Table 4 here

Utility model

The estimated utility associated with testing for *HLA-A*31:01* was greater, at 0.52 (95% CI, 0.19 to 1.00) than not testing at 0.33 (95% CI, -0.07 to 0.81). Consequently the choice model estimated the probability of test uptake at 55% (95% CI, 54 to 57) which would suggest that more patients would choose to be tested than not.

Patient-defined threshold for testing

The patient-defined threshold for testing for *HLA-A*31:01*, based on the rate of severe ADRs was 10.20 per 10,000 patients (95% CI, 10.11 to 10.33) which exceeds the actual number of severe ADRs identified through testing (7.28 per 10,000), suggesting that patients would accept a test.

Scenario analysis

Based on the characteristics of a test for *HLA-B*15:02* which, if implemented, is estimated to reduce the risk of serious ADRs by 6.94 cases per 10,000 patients treated, the probability of patient uptake is calculated as 61%. Total utility of testing was 0.32 compared with -0.13 for the untested cohort. The patient-defined threshold for testing is 16.55 severe ADRs per 10,000, implying that testing for *HLA-B*15:02* is also preferred, given that this value exceeds the true rate of serious ADRs of 9.70 per 10,000, if testing were implemented.

Two subgroups qualified for analysis, namely sex and age. Marginal rates of substitution indicated that females were more willing than males to trade a reduction in the chance of remission for reduction in the risk of the severe ADR. Females were willing to accept a 30.2 percentage point (95% CI, 19.5 to 52.9) reduction in remission for a 0.1% reduction in the risk of severe ADR, compared with

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males who were only willing to exchange a 4.6 percentage point (95%CI, 0.7 to 11.2) reduction in remission for the same 0.1% reduction in the risk of severe ADR. Differences in the rate of exchange for remission and side-effects (MRS) were not statistically significant for age.

Physicians' DCE

Eighty-three neurologists completed the questionnaire, the majority (n=69, 83%) were adult neurologists. Sixty-four (80%) respondents self-rated their knowledge of pharmacogenetic testing as 'No / Superficial Awareness', with just 16 (20%) reporting 'Detailed Awareness'. Fifty-six (67%) respondents had not requested any pharmacogenetic test in the previous year, while 21 had requested tests on up to 5 occasions. Forty-three (52%) respondents had reviewed at least one patient with a cutaneous ADR associated with carbamazepine in the previous year and 69 (83%) respondents had initiated carbamazepine in at least one patient in the previous month.

Thirteen neurologists were non-traders, defined as respondents who always select A or B ('test' or 'no test') throughout the experiment, regardless of changes in the profiles. Ten neurologists selected 'no test' to all responses and 3 neurologists selected 'test' to all responses. As discussed in the methods, pharmacogenetic testing is not currently mandatory and the decision whether to request a test will depend on a number of professional factors and personal opinions. During the individual interviews, a minority of neurologists were opposed to the introduction of pharmacogenetic testing into routine clinical practice, even when presented with attributes demonstrating a clear clinical benefit. In order to optimise our assessment of the attributes of a pharmacogenetic test valued by neurologists, we excluded non-traders from the analysis presented. However, the statistically significant attributes remained significant when non-traders were included in the model. The coefficients of all attributes with the exception of time to test result were significant and in the expected direction. Overall goodness of fit of the model was good. The odds that respondents selected the test decreased by 1% for every £1 increase in the cost of testing. An increase of 1 percentage point in PPV increased the odds of preferring pharmacogenetic testing by 7%; reference

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to *HLA-A*31:01* testing in the BNF increased the odds that respondents would test by 58%; and a test that predicts both severe and mild ADRs decreased the odds of testing by 31% (Table 4).

Marginal rates of substitution for the significant attributes indicated that neurologists were willing to pay £5.87 for a 1 percentage point increase in NPV and £3.99 for an equivalent increase in PPV. Respondents were willing to pay £31.29 for the coverage of mild in addition to severe cutaneous ADRs, and £39.35 for the inclusion of testing advice in BNF (Table 4).

Utility model

The total utility of testing for *HLA-A*31:01* is positive at 6.36 (95% CI, 3.74 to 10.22), indicating a general tendency to request the test (Table 5). Reducing the cost of testing from £100 to £35 increased the probability of requesting the test to 68.1%. A scenario in which the time to test result is reduced from 4 to 2 days had little influence on the probability of requesting the test, but an improvement in PPV from 26% to 70%, increased the probability of requesting the test almost 8-fold, to 88.6%. An improved NPV of 99% compared to the existing 96% increased the probability of requesting the test to 55.1%.

Insert Table 5 here

Discussion

Using a structured ranking exercise, we found that patients prioritised health outcomes relating to the benefits of treatment, in terms of seizure freedom and associated adverse events. The results of the DCE suggested that patients were willing to accept a less effective AED if that treatment had less risk of harm. They were willing to forego a 1,760 per 100,000 chance of improvement in remission for each 1 in 100,000 reduction in the risk of a severe ADR. When patient preferences were analysed alongside data of actual event rates and characteristics of a test for *HLA-A*31:01*, the results indicate that patients would prefer testing and being prescribed lamotrigine (conditional on test result) to the current standard of care. The current rate of ADR for patients who have the test

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is 7.28 per 10,000; if this were to increase by an additional 19 (or more) per 10,000, patients would prefer standard care.

In contrast to patients, neurologists highlighted process-related outcomes. Their preference for higher NPV might indicate a degree of caution in terms of wanting tests with a reduced likelihood of false negative results that would require the prescribing of a second choice AED. They were willing to pay an additional £58.67 per 10 percentage point increase in NPV. Neurologists were willing to pay an additional £39.35 for a test which was included in the BNF. This attribute captures tests that are recommended by regulatory agencies or included in clinical guidelines and are more likely to have high PPV and NPV [22]. A pharmacogenetic test that was less expensive was predictably preferred, but reduced turnaround time did not significantly influence the probability of requesting the test.

The study benefitted from having taken a systematic and rigorous approach to identifying attributes and levels that were both plausible and relevant to each perspective. For the DCE of patients, these were derived from interviews, with the final selection of attributes and levels piloted in cognitive interviews and presented in numerical and pictogram format to aid interpretation. A recent systematic review found that DCE studies have been notoriously poor at reporting the methodology supporting the explanation of risk and the validity of risk communication [23]. This study represents a thorough application of cognitive interviews to support the face validity of the design of the DCE and the presentation of risk attributes, and associated trading tasks. A comparable approach was taken with neurologists, which included a literature review and structured interviews, consistent with guidelines for DCE attribute selection [24].

Our inclusion of both patients' and clinicians' perspectives represents an important addition to the emerging literature on preference-elicitation in pharmacogenetics. The finding that both groups identified very different attributes but generally consistent preferences is reassuring in the context of implementing a new health technology. Patients' acceptance of a decrease in treatment benefit

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for a reduced chance of serious adverse drug reactions – even if that chance is very small – implies that patients will be satisfied with a prescription for a second choice AED which might not necessarily be as effective as the first.

Payne et al. [13] evaluated patient and health care professionals' preferences, using DCE methods, for pharmacogenetic testing of TPMT prior to treatment with azathioprine. Their study focused on service delivery and found that patients valued accurate and timely information about the necessity of the test and interpretation of the results. Our patient study differed as it focused on their preference for different AEDs, accepting that the key consequence of a pharmacogenetic test is the possibility of being prescribed an alternative medicine with a different safety profile, and potentially reduced effectiveness. We subsequently modelled the scenario of pharmacogenetic testing using additional information on the actual benefits of AEDs and test characteristics. This approach has the advantage of acknowledging the broader clinical context of testing as opposed to the specific action of whether or not to test. Importantly, we have derived the threshold at which patients' utility will be maximised through testing prior to taking carbamazepine.

We are aware of two other DCEs of patients with epilepsy. Lloyd et al. [11] used a DCE to elicit the importance of adverse events compared with seizure control for people with epilepsy and found that patients preferred AEDs with less severe adverse events, greater control and least cost. This direction of preferences was the same in our study, however, the amount of remission patients were willing to forego for a 1% reduction in rash differed: 4.45% seizure control for 1% reduction in risk of rash compared to a 0.58 percentage point reduction in remission for a 1 percentage point reduction in rash in our study. This may be explained by differences in how attributes were presented in the DCE, in our study we considered a 'potentially life threatening adverse drug reaction' that may influence the strength of preference for other attributes. Lloyd et al. [11] also included cost, whereas our study only focused on treatment benefits and harms. More recently, Manjunath et al. [12] included attributes for seizure frequency and, among others, 'short term' side effects

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(sleepiness, dizziness, headache, nausea, tremor, double or blurred vision, and skin rash) and 'long term' side effects (fatigue, moodiness, confusion or memory problems). Patients with epilepsy considered seizure reduction to be the top priority when ranked against the reduction or elimination of side effects. However as with Lloyd et al. [11], there was no consideration of more serious ADRs which respondents to our DCE considered important.

Our study had some limitations. The survey was conducted online which resulted in a self-selected sample of patients. This may affect the generalizability of the findings, particularly given that access to, and use of the internet will be variable among patients with epilepsy. Moreover, the sample primarily represented prevalent cases with long-standing experience of epilepsy, compared to incident cases who will be most commonly offered testing. In addition, the severity of epilepsy, defined as the frequency of seizures, was not recorded in the survey. It is foreseeable that patients with more severe epilepsy may be willing to trade a greater risk of ADR for an improvement in seizure control. Nevertheless, the agreement of our findings with other such studies lends support to the validity of the results. Common to all DCEs is the balance of comprehensiveness in the selection of attributes included and ability of respondents to make rational choices. Our DCE of patients was restricted to the 5 highest ranked attributes each with 2 levels, and only 5 patients did not select the choice which was marginally dominant and this had no impact on the result. By contrast, the DCE of physicians was somewhat more extensive with 6 attributes and 16 levels in total, and 13 respondents were non-traders. Overall, however, we considered the impact of the DCE designs not to have adversely affected the study conclusions. Finally, the study included a sample of UK patients and neurologists and the characteristics of these groups as well as the nationally funded healthcare system where patient care takes place, may limit the generalisability of results. In particular, the extent to which the results of the assessment of neurologists' preferences for pharmacogenetic testing can be extrapolated to other populations may be limited both by different healthcare systems (for example privatised systems) and different ethnic populations where the risk

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of ADRs associated with carbamazepine may be different. However, importance of the significant attributes of predictive accuracy (PPV, NPV) will likely translate across all populations.

In conclusion, our analysis of patient preferences indicates that patients value the reduction in risk of severe ADR which could be achieved by pharmacogenetic testing prior to prescribing carbamazepine. The DCE of neurologists would suggest that the most effective method of ensuring that current pharmacogenetic tests are used more widely would be for the cost of testing to reduce. Reassuringly, testing for *HLA-A*31:01* is cost-effective [25] meaning that turnaround time to result will likely become important given there is often a clinical urgency and patient expectation for treatment of uncontrolled seizures.

Acknowledgements: The authors wish to thank Ana Alfirevic and Vincent Yip (University of Liverpool), and Margaret Rawnsley and Angela Pullen (Epilepsy Action). The research is supported by the NIHR Research for Patient Benefit (RfPB) Programme: PB-PG-0909-20161 – Defining patient preferences and priorities for treatment options and outcomes in epilepsy (EAFH, RA, GAB, AJ, ADG, DAH); the MRC North West Hub in Trial Methodological Research (COP, DAH): G0800792; and the NIHR Academic Clinical Fellowship Programme (GP)

Declaration: The authors declare no conflict of interest and confirm to have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Contributions: GP, EAFH, MP, AGM, DAH contributed substantially to the conception and design of the work. All authors made contributions to the acquisition, analysis, or interpretation of data. GP,

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EAFH, DAH drafted the paper and all authors revised it critically for important intellectual content, and gave their final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B, Gamble C, Goulding PJ, Howell SJ, Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach JP, Nicolaides P, Roberts R, Shackley P, Shen J, Smith DF, Smith PE, Smith CT, Vanoli A, Williamson PR; SANAD Study group. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. Lancet 2007; 369: 1000-15.
2. Tudur Smith C, Marson AG, Chadwick DW, Williamson PR. Multiple treatment comparisons in epilepsy monotherapy trials. Trials 2007; 8: 34.
3. Kennedy GM, Lhatoo SD. CNS adverse events associated with antiepileptic drugs. CNS Drugs 2008; 22: 739-760.
4. Sekula P, Dunant A, Mockenhaupt M, Naldi L, Bouwes Bavinck JN, Halevy S, Kardaun S, Sidoroff A, Liss Y, Schumacher M, Roujeau JC; RegiSCAR study group. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. J Invest Dermatol 2013; 133: 1197-204.
5. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, Wu JY, Chen YT. Medical genetics: a marker for Stevens-Johnson syndrome. Nature 2004; 428: 486.
6. Chen P, Lin JJ, Lu CS, Ong CT, Hsieh PF, Yang CC, Tai CT, Wu SL, Lu CH, Hsu YC, Yu HY, Ro LS, Lu CT, Chu CC, Tsai JJ, Su YH, Lan SH, Sung SF, Lin SY, Chuang HP, Huang LC, Chen YJ, Tsai PJ, Liao HT, Lin YH, Chen CH, Chung WH, Hung SI, Wu JY, Chang CF, Chen L, Chen YT, Shen CY; Taiwan SJS Consortium. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med 2011; 364: 1126-33.
7. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperavičiūtė D, Carrington M, Sills GJ, Marson T, Jia X, de Bakker PI, Chinthapalli K, Molokhia M, Johnson MR, O'Connor GD, Chaila E, Alhusaini S, Shianna KV, Radtke RA, Heinzen EL, Walley N, Pandolfo M, Pichler W, Park BK,

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Depondt C, Sisodiya SM, Goldstein DB, Deloukas P, Delanty N, Cavalleri GL, Pirmohamed M. HLA-A*3101 and Carbamazepine-Induced Hypersensitivity Reactions in Europeans. N Engl J Med 2011; 364: 1134-43.

8. Shah J. Criteria influencing the clinical uptake of pharmacogenomic strategies. BMJ 2004; 328: 1482-6.
9. Ryan M, Farrar S. Using conjoint analysis to elicit preferences for health care. BMJ 2000; 320: 1530-3.
10. de Bekker-Grob EW, Ryan M, Gerard K. Discrete choice experiments in health economics; a review of the literature. Health Econ 2012; 21: 145-72.
11. Lloyd A, McIntosh E, Price M. The impacts of drug adverse effects compared with seizure control for people with epilepsy. Pharmacoeconomics 2005; 23: 1167-81.
12. Manjunath R, Yang JC, Ettinger AB. Patients' preferences for treatment outcomes of add-on antiepileptic drugs: a conjoint analysis. Epilepsy Behav 2012; 24: 474-9.
13. Payne K, Fargher EA, Roberts SA, Tricker K, Elliott RA, Ratcliffe J, Newman WG. Valuing pharmacogenetic testing services: a comparison of patients' and healthcare professionals' preferences. Value Health 2011; 14: 121-34.
14. Orme BK. Getting Started with Conjoint Analysis: Strategies for Product Design and Pricing Research. 2nd Edition: Research Publishers LLC, 2010.
15. Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. Neurology 2005; 64: 1134-8.
16. Joint Formulary Committee. British National Formulary. 68th ed. London: British Medical Association and Royal Pharmaceutical Society, 2014.
17. Summary of Product Characteristics for carbamazepine. Electronic Medicines Compendium. London: Datapharm Communications Limited, 2014.

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18. Hahn GJ, Shapiro SS. A catalog and computer program for the design and analysis of orthogonal symmetric and asymmetric fractional factorial experiments. Schenectady, New York: General Electric, Research and Development Center, 1966.
19. Yip VL, Marson AG, Jorgensen AL, Pirmohamed M, Alfirevic A. HLA Genotype and Carbamazepine0Induced Cutaneous Adverse Drug Reactions: A Systematic Review. Clin Pharmacol Ther 2012; 92: 757-65.
20. Lim KS, Kwan P, Tan CT. Association of HLA-B*1502 allele and carbamazepine-induced severe adverse cutaneous drug reaction among Asians, a review. Neurol Asia 2008; 13: 15-21.
21. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure for hypertension control. J Clin Hypertens 2008; 10: 348-54.
22. Kendall M, Enright D. Provision of medicines information: the example of the British National Formulary. Br J Clin Pharmacol 2012; 73: 934-8.
23. Harrison M, Rigby D, Vass C, Flynn T, Louviere J. Payne K. Risk as an attribute in discrete choice experiments: a systematic review of the literature. Patient 2014; 7(2): 151-70.
24. Coast J, Al-Janabi H, Sutton EJ, Horrocks SA, Vosper AJ, Swancutt DR, Flynn TN. Using qualitative methods for attribute development for discrete choice experiments: issues and recommendations. Health Econ 2012; 21: 730-41.
25. Plumpton CO, Yip VLM, Alfirevic A, Marson AG, Pirmohamed M, Hughes DA. Cost-effectiveness of screening for HLA-A*31:01 prior to initiation of carbamazepine in epilepsy. Epilepsia 2015. doi: 10.1111/epi.12937

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Figure 1: Example of binary choice DCE questions

Physician DCE

Question: "You have decided to prescribe carbamazepine for your patient. You may either select the following pharmacogenetic test prior to the prescription, or select not to test and proceed with the prescription blindly"

Cost	£35
Days to result	2
Positive predictive value (PPV)	2%
Negative predictive value (NPV)	70%
Coverage	Serious ADRs ONLY
Inclusion in British National Formulary (BNF)	Yes

☐ I WOULD select the test prior to the prescription of carbamazepine

☐ I WOULD NOT select the test and proceed with the prescription of carbamazepine blindly

Patient DCE

Question: "Which medication would you prefer?"

	MEDICATION A	MEDICATION B
Stop Seizures *One year after starting this medication*	5 in 10 people seizures stop	3 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	3 in 10 people experience fewer seizures	1 in 10 people experience fewer seizures
Mild skin rash *A blotchy, itchy red rash on your upper body*	1 in 100 people experience a mild skin rash	26 in 100 people experience a mild skin rash
Memory Problems *These are frequent and affect activities of daily life*	1 in 100 people experience memory problems	7 in 100 people experience memory problems
Potentially life-threatening reaction *Severe skin reaction that may cause death*	**UNCOMMON** More than 1 in 1000 people experience a life-threatening reaction	**RARE** More than 1 in 10,000 people experience a life-threatening reaction
Which medication would you prefer to take?	☐	☐

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Table 1: Attributes and levels of the discrete choice experiments

Attribute	Description	Levels (code)	Rationale
Physicians' DCE			
Cost of Test	The total cost of the pharmacogenetic test in Pounds Sterling.	35 (0) 100 (1) 200 (2)	Cost attribute ranked highly by neurologists. Realistic levels based on expert opinion (M Pirmohamed).
Time to Result	The total time from initially requesting the pharmacogenetic test to receipt of result.	2 (0) 4 (1) 7 (2)	Time attribute ranked highly by neurologists. Realistic levels based on expert opinion (M Pirmohamed).
Positive Predictive Value (PPV)	The probability of experiencing the ADR if a positive result is identified on the pharmacogenetic test: the 'true positives'.	2 (0) 35 (1) 70 (2)	PPV attribute ranked highly by neurologists. Range of PPV values informed by literature review [5-7]
Negative Predictive Value (NPV)	The probability of not experiencing the ADR if a negative result is identified on the pharmacogenetic test: the 'true negatives'.	70 (0) 85 (1) 99 (2)	NPV attribute ranked highly by neurologists. Range of NPV values informed by literature review [5-7]
Coverage of Test	The ability of the pharmacogenetic test to predict severe ADRs only, or mild in addition to severe ADRs.	Severe Hypersensitivity Adverse Drug Reactions (0) Severe AND Mild Hypersensitivity Adverse Drug Reactions (1)	Parameter informed by the attributes of current alleles: *HLA-A*31:01* is associated with severe and mild ADRs [7], *HLA-B*15:02* is associated with severe ADRs only [5]
British National Formulary (BNF)	The inclusion or exclusion of the pharmacogenetic test in the drug information detailed under carbamazepine.	Test NOT INCLUDED in the BNF (0) Test INCLUDED in the BNF (1)	Regulatory approval and inclusion in clinical guidelines ranked highly by neurologists. Inclusion in the British National Formulary [16] was included in the DCE as a pragmatic marker of regulatory approval and clinical availability.
Patients' DCE			
Seizures Stop	The probability of patients achieving 1-year remission from seizures with AED	5 in 10 people (0.5) 3 in 10 people (0.3)	Primary outcome of AED studies is 12 month remission. Levels based on published clinical trial data [1].
Fewer seizures	The probability of patients experiencing	3 in 10 people (0.3)	Seizure reduction was the highest ranked outcome

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	fewer seizures after 1-year with AED	1 in 10 people (0.1)	by patients. Levels based on clinical trial data [1].
Mild skin rash	The probability of patients experiencing a mild adverse drug reaction but which is sufficient to warrant change in AED	1 in 100 people (0.01) 26 in 100 people (0.26)	*HLA-A*31:01* allele is associated with mild hypersensitivity reaction with patients exposed to carbamazepine. Levels based on published data [1,7].
Memory problems	The probability of patients experiencing memory problems which are sufficient to warrant change in AED	1 in 100 people (0.01) 7 in 100 people (0.07)	Adults with established epilepsy and prescribing clinicians were most concerned about memory problems in ranking exercises. Levels based on published clinical trial data [1].
Potentially life-threatening reaction	The probability of patients experiencing a rare but severe skin reaction, described as hot, painful patches on the skin that can blister and risks death.	RARE: More than 1 in 10 000 people (0.0001) UNCOMMON: More than 1 in 1000 people (0.001)	*HLA-A*31:01* allele is associated with Drug Induced Hypersensitivity Syndrome (DIHS), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) with patients exposed to carbamazepine. Levels based on published data on allele associations [7] and SmPC for carbamazepine [17].

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Table 2: Values of regression variables used to estimate utility, probability of test uptake and maximally tolerated rate of severe ADR for patients to prefer testing. Data are taken from source, or derived according to standard epidemiological calculations.

	Expected probabilities conditional on AED and *HLA-A*31:01* test result			Testing Strategy		Reference
Attributes	CBZ / -ve	CBZ / +ve	LTG / +ve	Test	No test	
Remission	36.000	36.000	29.000	35.8189	36.0000	[1]
Fewer seizures	17.370	17.370	21.430	17.4751	17.3700	[1]
Memory problems	3.1746	3.1746	2.6455	3.1609	3.1746	[1]
Skin rash	7.000	34.000	4.000	6.9224	7.6986	[1,7]
Severe ADR	0.0738	1.0895	0.0354	0.0728	0.1001	[7,15,17]

All data are reported as number of events per 100 patients.

Abbreviations: AED is anti-epileptic drug; CBZ is carbamazepine; LTG is lamotrigine; ADR is adverse drug reaction

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Table 3: Patient characteristics

Patients' characteristics	n	%
Age: median (range)	38	(18-72)
Female	61	66.3
Time since diagnosis:		
Less than 4 months	1	1.1
4-12 months	3	3.3
1-5 years	14	15.4
6-10 years	12	13.2
More than 10 years	61	67.0
Seizure type:		
Focal	27	31.4
Complex focal	40	46.5
Absences, tonic, atonic	45	52.3
Tonic clonic	56	65.1
Time since last seizure:		
Less than a week	38	44.2
Less than a month	16	18.6
Less than 6 months	14	16.3
Less than a year	2	2.3
A year or over	16	18.6
Seizure frequency compared to 1 year ago:		
More often	19	22.1
Less often	26	30.2
About the same	41	47.7
Prescribed AED in past 3-months	85	98.8
Changes to AED in past 3-months:		
No change	54	63.5
Increased/decreased	25	29.4
Change of drug	9	10.6
Additional drug	12	14.1
Fewer drugs	2	2.4
Stopped altogether	1	1.2
Reason for changes:		
Lack of seizure control	30	90.9
Unpleasant side effects	14	42.4
Remission	1	3.0
Morisky non-adherence [21]	16	50.0
Experience of taking CBZ	31	36.5
Experience of adverse events:		
Change or stop due to memory problems	8	24.2
CBZ skin rash	10	18.5
CBZ severe ADR (requiring hospital treatment)	1	1.9
Living alone	13	15.9

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In employment, education, or looking after home	49	60.5
Ethnicity:		
White	74	90.2
Black / African / Caribbean / Black British	3	3.7
Asian / Asian British	1	1.2
Mixed / Multiple ethnic groups	2	2.4

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Table 4: Random effects logit regression model and marginal rates of substitution

DCE of patients			
Attribute	**Coefficient (95% CI)**	**Odds ratio**	**Remission (95% CI)**
Remission	0.037 (95% CI 0.032 to 0.054	1.04	1.00
Fewer seizures	0.011 (95% CI 0.003 to 0.024)	1.01	0.29 (95% CI 0.07 to 0.58)
Memory	-0.119 (95%CI -0.182 to -0.104)	0.89	-3.22 (95% -4.54 to -2.35)
Skin rash	-0.021 (95% CI -0.034 to -0.016)	0.98	-0.58 (95% CI -0.84 to -0.38)
Severe ADR	-6.490 (95% CI -10.295 to -5.467)	0.00	-175.83 (95% CI -253.30 to -121.42)
Constant	0.147 (95% CI -0.022 to 0.392)	1.16	
Pseudo-R^2 = 0.2118; Wald χ^2 140.34; Log likelihood = -382.74; p=0.00			
DCE of neurologists			
Attribute	**Coefficient (95% CI)**	**Odds ratio**	**Willingness to pay (95% CI)**
Cost	-0.012 (95% CI -0.016 to -0.010)	0.99	- -
Time to Result	0.027 (95% CI -0.077 to 0.131)	1.03	- -
PPV	0.047 (95% CI 0.042 to 0.061)	1.05	3.99 (95% CI 3.00 to 5.37)
NPV	0.068 (95% CI 0.056 to 0.096)	1.07	5.87 (95% CI 4.04 to 8.46)
Coverage of Test	-0.365 (95% CI -0.774 to -0.095)	0.69	-31.29 (95% CI -60.06 to -7.20)
Included in BNF	0.459 (95% CI 0.140 to 0.865)	1.58	39.35 (95% CI 10.97 to 71.05)
Constant	-7.120 (95% -9.879 to -5.824)		
Pseudo-R^2 value 0.2294; Wald χ^2 199.74; Log likelihood = -529.66; p<0.001			

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Table 5: Results of scenario analysis of varying attribute levels within plausible ranges on the total utility and probability of test uptake

Parameter	Attribute and levels	Utility	Probability of uptake
Base case	Cost: £100 Time to result: 4 Days PPV: 26% NPV: 96% Coverage of test: Severe and mild Included in BNF: No	6.3584 (95% CI: 3.7391 – 10.2210)	49.9%
Reduced cost	Cost: £35	7.117 (95% CI: 4.8012 – 10.8525)	68.1%
Reduced time to result	Time to result: 2 Days	6.3046 (95% CI: 3.8939 – 9.9629)	48.6%
Improved PPV	PPV: 70%	8.4055 (95% CI: 5.5658 – 12.8900)	88.6%
Improved NPV	NPV: 99%	6.5639 (95% CI: 3.9072 – 10.5111)	55.1%

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